Amendments to the Specification:

Please amend the specification as follows.

Using the paragraph numbering of the published application for convenience and clarity, please replace the following numbered paragraphs with the following:

[0012] Commercial preparations of IFN-β are approved for the treatment of patients with MS and are sold under the names ~~**Betaseron®**~~. **BETASERON®** (also termed ~~**Betaferon®**~~. **BETAFERON®** or IFN-β 1b_{ser17}, which is non-glycosylated, produced using recombinant bacterial cells, has a deletion of the N-terminal methionine residue and the C17S mutation), ~~**Avonex®**~~ **AVONEX®** and ~~**Rebif®**~~ **REBIF®** (also termed IFN-β 1a, which is glycosylated, produced using recombinant mammalian cells. Further, a comparison of IFN-β 1a and IFN-.β 1b with respect to structure and function has been presented in Pharm. Res. 15:641-649, 1998.

[0017] The isolated IFN-β mutein of the present invention is preferably a synthetic or recombinant IFN-β polypeptide, and can be a variant of a biologically active, native IFN-β, *e.g.*, human IFN-β and, more preferably, human IFN-β 1b. In particular, the isolated IFN-β mutein of the present invention can be a human IFN-β mutein and, more preferably, ~~**Betaseron®**~~. **BETASERON®** (also termed ~~**Betaferon®**~~. **BETAFERON®** or IFN-β 1b_{ser17}). The pharmaceutical compositions of the present invention can be stabilized, human serum albumin-free (HSA-free) pharmaceutical compositions. More particularly, the stabilized, HSA-free pharmaceutical compositions of the present invention can comprise an IFN-β mutein that is substantially monomeric and solubilized in a low-ionic-strength formulation.

[0023] In another aspect, the isolated IFN-β mutein of the present invention is ~~**Betaseron®**~~. **BETASERON®**).

[0028] FIG. 1 is a schematic illustrating the ~~**Betaseron**~~. **BETASERON®** dose escalation scheme using 250 mcg or higher-dose 500 mcg ~~**Betaseron**~~. **BETASERON®** in MS patients over a period of 12 weeks (see Example 1).

[0029] FIG. 2 is a schematic illustrating the baseline demographics of the MS patients randomized to either a 250 mcg or higher-dose 500 mcg ~~**Betaseron**~~. **BETASERON®**dosing regimen (see Example 1).

[0030] FIG. 3 is a schematic illustrating that, with respect to primary outcome adverse events (AEs), higher-dose 500 mcg ~~**Betaseron**~~. **BETASERON®** is safe and well-tolerated as compared to the 250 mcg dose of ~~**Betaseron**~~. **BETASERON®** (see Example 1).

[0031] FIG. 4 is a schematic illustrating that the dose escalation scheme for higher-dose 500 mcg ~~**Betaseron**~~. **BETASERON®** is at least as successful as the dose escalation scheme for 250 mcg ~~**Betaseron**~~. **BETASERON®** in MS patients, where over 90% of the patients attained the full, higher-dose 500 mcg ~~**Betaseron**~~. **BETASERON®**during the course of the study (see Example 1).

[0032] FIG. 5 is a schematic illustrating the median percent change from baseline (BL) of the T2 lesion number in MS patients receiving 250 mcg dose and higher-dose 500 mcg ~~**Betaseron**~~. **BETASERON®** (see Example 1).

[0033] FIG. 6 is a schematic illustrating the median percent change from baseline (BL) of the T2 lesion volume in MS patients receiving 250 mcg dose and higher-dose 500 mcg ~~**Betaseron**~~. **BETASERON®** (see Example 1).

[0035] The standard dose of IFN-β (*e.g.*, ~~**Betaseron®**~~. **BETASERON®**.) approved for use in the treatment of MS is 250 mcg. However, the maximum therapeutically effective dose of IFN-β has not previously been known. Also, it has not previously been known whether higher doses of IFN-β lead to improved efficacy for treatment of a patient with MS. Further, previous studies by others teach that doses higher than the approved amount are not well-tolerated in MS patients (see *e.g.*, Knobler et al., J. Interferon Res. (1993) 13: 333-340). However, contrary to the teachings of others, the present invention provides a new, higher therapeutically effective amount of an IFN-β mutein that is safe, well-tolerated and shows a positive trend towards beneficial effects for use in the treatment of patients with MS, and this dose is higher than the approved, standard dose of IFN-β. Thus, the pharmaceutical compositions and methods of the present invention can increase the possibility of benefits from treatment of MS using IFN-β and, also, the number of patients that benefit from treatment.

[0048] As used herein "patient" refers to a subject, preferably a human, who is in need of treatment. For example, a subject having MS or symptoms associated with MS is a patient in need of treatment of MS or associated symptoms of MS. A patient can be pre-treated for MS with a pharmaceutical composition or can be a naive patient who has not been pre-treated for MS with a pharmaceutical composition, prior to treatment with the higher-dose pharmaceutical composition or methods of the present invention. For example, a pre-treated patient can be one who has been pretreated with a different amount of an interferon or IFN-β mutein, *e.g.*, a standard approved dose (*e.g.*, 250 mcg ~~**Betaseron**~~. **BETASERON®**) prior to treatment with the higher-dose pharmaceutical compositions or methods of the present invention. For example, an approved dose of ~~**Betaseron®**~~. **BETASERON®**., ~~**Avonex®**~~ **AVONEX®**, or ~~**Rebif®**~~ **REBIF®**) can be used to pre-treat patients. The pharmaceutical compositions and methods of the present invention are suitable for use in the treatment of pre-treated and naive patients.

[0056] Combination therapies with other drugs, which are effective in the treatment of MS and have a different adverse event profile may increase the treatment effect and level out the adverse event profile. Suitable examples of combination therapies include, but are not limited to, *e.g.*, glatiramer acetate (~~Copaxone~~ **COPAXONE®**), mitoxantrone, cyclophosphamide, cyclosporine A, cladribine, monoclonal antibodies (*e.g.*, ~~Campath-H1®~~ **CAMPATH H1®** or ~~Antegren G~~ **ANTEGREN G®**/~~Natazulimab®~~ **NATAZULIMAB®**), and statins.

[0062] The IFN-β muteins of the present invention also muteins of a mature human, native IFN-β sequence (*e.g.*, IFN-β 1b), wherein one or more cysteine residues that are not essential to IFN-β biological activity have been deliberately deleted or replaced with other amino acids to eliminate sites for either intermolecular crosslinking or incorrect intramolecular disulfide bond formation. IFN-β muteins of this type include those containing a glycine, valine, alanine, leucine, isoleucine, tyrosine, phenylalanine, histidine, tryptophan, serine, threonine, or methionine substituted for the cysteine found at amino acid 17 of the mature native IFN-β amino acid sequence. Serine and threonine are the more preferred replacements because of their chemical analogy to cysteine. Serine substitutions are most preferred. An example of an amino acid sequence of an IFN-β mutein of the present invention is SEQ ID NO: 2. In a preferred embodiment, the IFN-β mutein is ~~Betaseron®~~. **BETASERON®**. (see *e.g.*, U.S. Pat. Nos. 4,588,585; 4,959,314; 4,737,462; L. Lin (1998) Dev. Biol. Stand. 96: 97-104).

[0107] In another preferred embodiment, the IFN-β mutein of the present invention is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by subcutaneous injection. For example, the IFN-β mutein can be manufactured by bacterial fermentation of a strain of E. coli that ~~carrys~~ **carries** a plasmid encoding the mutein. In a preferred embodiment, the IFN-β mutein is human interferon beta-$1b_{ser17}$ser17 (i.e., ~~Betaseron®~~. **BETASERON®**./~~Betaferon®~~. **BETAFERON®**).

WASH_1839494.2

[0108] In another preferred embodiment, IFN-β $1b_{ser17}$ is 165 amino acids in length, has a molecular weight of approximately 18,500 daltons. In another preferred embodiment, the IFN-β $1b_{ser17}$ polypeptide is made by isolating the native human IFN-β 1b gene from human fibroblasts and substituting the serine at position 17 with cysteine. In another preferred embodiment, the specific activity of IFN-β $1b_{ser17}$ is approximately 32 million international units (IU)/mg. In a preferred embodiment, ~~**Betaseron®**~~. **BETASERON®**.) (IFN-β $1b_{ser17}$) is supplied as a lyophilized powder containing a higher therapeutically effective amount of IFN-$\beta 1b_{ser17}$, and human albumin USP (United States Pharmacopoeia) and mannitol USP as stabilizers. In one embodiment, the stabilizers are human albumin USP and dextrose USP. In one preferred embodiment, the lyophilized protein product is a sterile, white to off-white powder that is intended for subcutaneous injection after reconstitution with a diluent supplied (*e.g.*, the diluent can be a sodium chloride solution, preferably a 54% solution of sodium chloride).

[0113] This Example illustrates the safety, tolerability, and positive trend towards beneficial effects of 500 mcg versus 250 mcg ~~**Betaseron**~~. **BETASERON®** (IFN-β $1b_{ser17}$) administered subcutaneously every other day (eod) in naive MS patients. The effects of 500 mcg versus 250 mcg of ~~**Betaseron**~~. **BETASERON®** were measured by magnetic resonance imaging (MRI) criteria, including gadolinium enhancing lesion number and combined unique lesion activity, in patients with relapsing-remitting MS. Using MRI parameters to monitor the effects of higher-dose ~~**Betaseron**~~. **BETASERON®** in the treatment of patients with MS, the findings of this study indicate a positive trend towards the beneficial effects of 500 mcg ~~**Betaseron**~~. **BETASERON®** as compared to the currently approved 250 mcg dose of ~~**Betaseron**~~. **BETASERON®**. Thus, the results of this study demonstrate the safe, well-tolerated, and positive trend towards beneficial effects of administering 500 mcg subcutaneous dose IFN-β $1b_{ser17}$ eod to patients with RRMS.

[0114] Design/Methods: A multicenter, randomized, double-blind, parallel group study comparing ~~Betaseron~~. **BETASERON®** (IFN-β 1b$_{ser17}$ser17) 500 mcg with 250 mcg, self-administered by subcutaneous injection eod for at least 12 weeks. Patients were instructed to use auto-injectors to give consistency of injection technique. The ~~Betaseron~~. **BETASERON®** was escalated over the first 6 to 12 weeks, and then maintained at full-dose for the duration of the study until the last randomized patient finished 12 weeks of treatment (see FIG. 1). Non-steroidal anti-inflammatory drugs were administered concomitantly with ~~Betaseron~~. **BETASERON®** injections to minimize flu-like symptoms. The safety and tolerability of the drug at the 500 mcg and 250 mcg dose was defined by the proportion of patients in each treatment arm experiencing flu-like syndrome, fever, myalgia, injection site reactions, asthenia, headache, and liver and bone marrow function abnormalities.

[0115] The first phase of this study compared the effect of ~~Betaseron~~. **BETASERON®** at doses of 250 mcg and 500 mcg on various brain MRI measures including the frequency of enhancing lesions and combined unique lesion activity. All patients also underwent gadolinium enhanced (0.1 mmol/kg) MRI scanning at baseline and week 12 according to a standardized protocol, and the MRI scans were analyzed in a blinded fashion.